DETAILED ACTION

The Applicants Amendments to the claims received on 7/22/2009 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 1/30/2009 are hereby withdrawn.

Claim(s) 3-8, 12, 16, 20-30 are pending. Applicants have amended claim(s) 8, 12, 16, and added new claims 29 and 30. Claims 3-7 are withdrawn. Claims 8, 12, 16, 20-30 are hereby examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976);In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

Claims 8, 12, 16, and 20-28, and the new Claims 29 and 30, stand rejected under 35 U.S.C. 103(a) as being unpatentable over Armour Pharmeceutical Company (EP 0115627) referred to as APC, and Moise Azria et al U.S. Patent 5,759,565, both from Applicant's IDS and made of record in the previous office action, and Grebow et al US Patent 5,026,825.

In instantly claimed invention is drawn to a composition consisting: an aqueous solution of calcitonin salmon at a concentration of 0.0355% w/w or 2,200 International Units (I.U.) per ml; Chlorobutanol at a concentration of about 0.25% to about 0.4% weight/weight; sodium chloride at a concentration of 0.85% weight/weight; a pH between 3 to 4; less than 5% oxygen; wherein the composition is suitable for intranasal administration in humans.

Azria et al teaches calcitonin in a saline solution (tonicity) of 0.75 % w/w which is about 0.85%, and at a pH of 3 to 5, see Claims 1 and 18 of Azria et al for example. The composition(s) taught are for nasal administration. The amount of calcitonin used in the invention is taught to be between 150 and 8,000 MRC units (I.U. of Activity) of salmon calcitonin, readable on Applicant's 2200 I.U. per ml. The composition is taught to be to

be stored under an inert Nitrogen atmosphere (an oxygen depleted environment) for stability of the calcitonin. Chlorbutanol is also taught as being use in the nasal composition but suffers from some drawbacks when used at concentrations above 0.6%. Azria et al does not teach the use of Chlorbutanol at ranges instantly claimed. The difference between what is taught by Azria et al and that of the prior art is Azria teaches that concentration of chlorobutanol above 0.6% have undesired effects but does not teach concentration ranges of chlorobutanol of between about 0.25% to 0.4% w/w.

APC teaches pharmaceutical composition for nasal administration comprising calcitonin at a concentration range from 1 to 150 µg/ml where the concentration and dosage levels of calcitonin are with a potency of about 4000 I.U. per mg, well within the range taught by Azria et al and instantly claimed. APC teaches the use of a Tonicity Adjuster in the range of 0.01-0.5 %w/v readable upon the saline solution of Azria et al. APC also teaches the use of Chlorobutanol (a preservative) in the range of 0.001-2.0 % w/v which is in the range instantly claimed, see page 5 and line 5-18 and page 6 for the additive ranges; note that the examiner is taking the mass of water to be 1 g/ml therefore which makes the translation fro w/v% to be essentially identical to that of w/w%.

Grebow et al, US Patent 5,026,825 teaches an intranasal composition comprising from about 0.0001% W/V to about 15% W/V of a polypeptide salmon calcitonin or a polypeptide having calcitonin activity (potency of from about 100 to about 10,000 international units per mg of polypeptide readable upon Applicant 0.355% w/w of

Claim 8 and 2200 I.U of Claim 12 and 16, see Claims 1-7 of '825. Grebow further teaches the preservative Chlorobutanol in ranges from 0.5-1.0 and in Example 9, teaches Chlorobutanol at 0.1% w/v. Note that the examiner is taking the mass of water to be 1 g/ml therefore which makes the translation from w/v% to be essentially identical to that of w/w%. Further note that while Grebow teaches ranges from 0.5-1.0 %w/v. in column 12, but has a specific example using 0.1% w/v, which makes the effective range 0.1-1.0% readable on the instant ranges claimed.

It would have been obvious at the time of the instantly claimed invention to use concentrations of chlorobutanol as a preservative at %w/v concentrations below that of 0.6% to prevent any deleterious effects in the composition as the art clearly teaches the use of Chlorobutanol in combination with calcitonin, and at concentrations as low as 0.1% w/v as taught by Grebow et al. The prior art references clearly shows the use of chlorobutanol in combination with calcitonin and at the pH ranges instantly claimed. It would have been obvious to one skilled in the art at the time of invention to determine all operable and optimum components in the claimed composition of U.S. Patent No. Armour Pharmeceutical Company (EP 0115627) and Moise Azria et al U.S. Patent 5,759,565, because the component % w/v are an art-recognized result-effective variable that is routinely determined and optimized in the composition arts. One would have been motivated to modify the composition as taught by both APC, Azria et al, and Grewbow to optimize the concentration parameters to eliminate undesirable effect of any given component and or enhance the effect of a given component as calcitonin, saline, Chlorobutanol, as the art teaches both their combination and use, and within the

ranges instantly claimed. While the prior art is silent on the composition being at less than 5% oxygen, it is the Examiner's position that oxygen would be less than 5% in the composition(s) taught by the art because oxygen is quite insoluble and envisioning even the upper end of 5% (5 g of 0_2 per 100 ml of water) is rather difficult. The storing of the compositions under inert condition (under a Nitrogen atmosphere) is readable upon having the O_2 concentration below 5%, if not totally eliminating the presence of O_2, as taught by Azria et al. Given the intended use of the composition is for nasal administration, putting the composition into a sprayer is obvious and readable upon Claims 20-28. The parameters of the actuator tip, spray pattern, droplet size etc... are also art-recognized result-effective variables that are routinely determined and optimized for nasal administration in the composition arts. The limitations of Claims 20-28 are a function of the applicator and do not have patentable weight on the composition itself. Just because the device can spray at a particular angle and produce droplets of a certain size does not alter the composition over the prior art because the device will spray any liquid at those desired angles and droplet size. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicant's Arguments

Applicants have argued again that the Azria et al reference is an explicit teaching away from the use of chlorobutanol, see page 7 of the remarks. It is further argued from the M.P.E.P., that obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. It is argued that the Azria et al reference showed insufficient activity at 0.6%, and with the prior Declaration by H.T. Constantino, it is argued again that it was ineffective at 0.6% or less. It is also argued that the chlorobutanol attacked the rubber stopper for the spray device, providing a motivation to not use chlorobutanol.

It is further argued that the language of the instant claims is "consisting," and thus the references cannot be considered prior art because they teach additional components in their compositions that have the same instantly ingredients claimed. It is further argued that the Azria et al reference became available to the art much later than either APC or Grebow, and that these references disclosed a number of possible preservatives for use in calcitonin formulation, which would not inform one of skill in the art which one to use and at what concentrations.

Next, Applicants turn to Grebow and argue that they teach the chlorobutanol at lower concentrations than instantly claimed, and that chlorobutanol is used with another preservative and when considered together, their combined concentration is lower that that instantly claimed. Since Applicant's are using the phrase "consisting" rather than "comprising," the prior art which has two preservative must be excluded as prior art

because it does not teach the limited ingredients instantly claimed with chlorobutanol as the single preservative.

Lastly, it is argued that the pharmaceutical device that sprays the instantly claimed ingredients at the claimed patterns and droplet sizes, and argue that the burden is on the examiner to explain why the such a device would be not be obvious.

Response to Applicants Arguments

Applicants arguments have been carefully considered but are not deemed persuasive to overcome the rejection. Regarding Applicants' arguments that Azria et al teaches away from the use of chlorobutanol (and with excessive bolding and underlining which does nothing to change the meaning of the statements that are copied from the Azria et al reference), it is clear from Azria et al that chlorobutanol has a deleterious effect at 0.6% and higher, but there is no indication that this would be true for concentrations lower that the 0.6% that Azria et al teaches, and this is supported by the secondary references which used chlorobutanol at lower concentrations. Just because one reference teaches an ingredient to have deleterious properties at a particular concentration (and logically at higher conventions regardless if not explicitly stated), in this case, Chlorobutanol, it is not an explicit teaching away from its use at lower concentrations. The prior art demonstrates this as both APC and Grebow clearly teach calcitonin with chlorobutanol in the ranges claimed, and also teach a specific example where chlorobutanol is used at much lower concentrations as a preservative which would not destroy the rubber stopper at those lower concentration.

The arguments regarding the consisting and comprising limitations do not overcome the rejection because the chlorobutanol is taught to be used in combination with calcitonin, and the fact that the prior art has other ingredients besides those instantly claimed does not make the combination of calcitonin with chlorobutanol unobvious. The fact that the APC reference and Grebow teach other preservative is also not a consideration for the use of chlorobutanol as Grebow presents a specific example that has chlorobutanol as the ingredient for a preservative, regardless of the fact it had other ingredients in the composition.

Regarding the use of a device that sprays the instantly claimed composition, which is the invention, it is mere judicious selection of a device to spray the composition, as Applicants have not invented the device, but have made use of a device that which is already known in the art. Thus it is judicial selection of the device to spray the calcitonin into the nasal cavity. Applicants have stated in the specification:

> The amount of calcitonin to be administered according to the method of the present invention will depend upon the particular calcitonin chosen, the condition treated, the desired frequency of administration and the effect desired. Generally the concentration of calcitonin in solution should be about 2200 International Units (I.U.) per ml. If 0.09 mL is administered per actuation, this administers 200 I.U. to the patient. The International Units are based upon a bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute of Biologic Standards and Control.
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> For the purposes of nasal administration, the calcitonin solutions of the present invention will be placed in a nasal applicator device. Suitable applicators are known in the art and include those adapted for administration of liquid compositions to the nasal mucosa in drop or spray form. Since dosing with calcitonins should be as accurately controlled as possible use of spray applicators for which the administered quantity is susceptible to precise regulation will generally be preferred. Suitable administrators include atomizing devices such as pump-atomizers and aerosol dispensers. The atomizing device will be provided with an appropriate spray adaptor allowing delivery of the calcitonin solution to the nasal mucosa.

Applicants have not invented a new device to deliver the composition at the claimed spray pattern with the major axis being about 31.2 mm and the minor axis being about 27.4 mm, etc, so the device is a choice of the skilled artisan. Thus, the device makes no contribution to the patentability of the invention as Applicants are on record as stating these deices are known in the art.

The composition instantly claimed is one of ingredients already shown to be used in combination with one another, and the combination instantly claimed have not shown any unexpected result. Therefore, from the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prior art contained in the reference of record can be applied in the next office action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas S. Heard** whose telephone number is **(571) 272-2064**. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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